by these amendments.

Remarks

Examiners' Interview (June 2, 1994) and Summary of current Office Action

Applicants would like to first thank Examiners Salata and Moezie for the Interview held on June 2, 1994, with co-inventors, Dr. Gary Ott and Dr. Gail Barchfeld, on the above-identified application.

Claims 1-9 and 29, and 36 are pending in the present application. As reflected in the current Office Action, the only remaining issue is the rejection under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103 as obvious over either Glass, et al., U.S. 3,919,411 or Cantrell, et al., U.S. 4,803,070. Applicants acknowledge the withdrawal of the previous 35 U.S.C. 102(b)/103 rejection over Prigal, U.S. 3,678,149.

As applicants are submitting material that puts the application in condition for allowance, applicants respectfully request that this Amendment be entered. To this end, applicants are submitting herewith a Declaration under 37 C.F.R. 1.132, as discussed during the Interview, wherein the present invention is shown to be novel and nonobvious over the cited art.

The Present Invention

The present invention relates to new submicron oil-in-water emulsion formulations having utility as adjuvants. At present, these proprietary adjuvants have been tested in over 4,000 individuals in many clinical trials with a variety of antigens (e.g., herpes simplex virus glycoproteins, human immunodeficiency virus gp120, influenza proteins, cytomegalovirus glycoproteins).

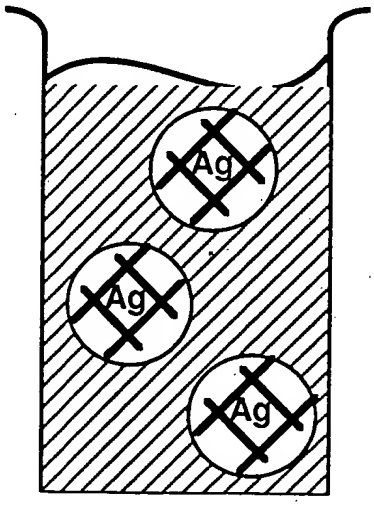
Rejection under 35 U.S.C. 102(b)/103

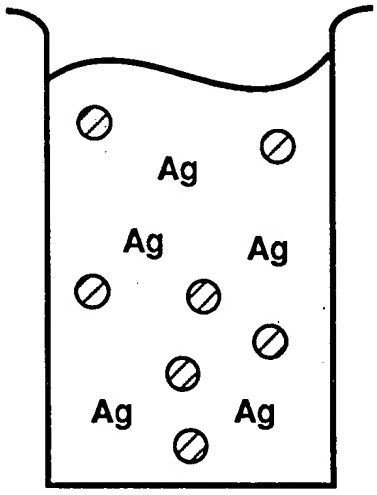
Neither Glass nor Cantrell teaches or suggests submicron oil-in-water emulsions. In fact, Glass relates to an entirely different family of adjuvants requiring a high percentage

of oil and antigen-binding polymeric resins. Glass describes the use of a macromolecular synthetic resin in a water and oil emulsion wherein the oil component "must be about 25 percent by volume of the total system, with a maximum of about 85 percent" (U.S. 3,919,411, column 5, lines 59-62). This type of adjuvant has very different physical properties from those emulsions claimed by applicants.

Additionally, Glass refers to the "depot action" of its viscous (thick) formulation. As explained during the Interview, adjuvants can work by a variety of mechanisms, such as extended release (depot effect), in vivo transport, and direct immunostimulation. Depot effect refers to the deposit of any physical material that holds the antigen at the injection site whereby the antigen is slowly released from this site. Glass discloses an emulsion "bolus" that holds the resin at the injection site for slow release. In fact, Glass is basically a variation on incomplete Freund's adjuvant (IFA) with the required addition of a synthetic resin matrix to bind antigens for a very slow release.

On the other hand, applicants' emulsions do not serve as depots for antigen release but instead the antigen, as well as the adjuvant, is rapidly dispersed from the site of introduction, resulting in direct immunostimulatory effects. There is no "bolus" holding the antigen at the site. Schematically, a comparison of the Glass formulations (e.g., Example 3, Example 5) with that of applicants appears as:





where the diagonal lines represent oil phase (either as a droplet or as the medium, depending upon the formulation), Ag is the antigen of choice, circles represent droplets (either oil or water, depending upon the formulation), and the grids represent the Glass resin.

In sum, there is no teaching or suggestion from Glass that would direct one to formulate low viscosity, oil-in-water emulsions having direct immunostimulatory effects from a reference suggesting predominantly water-in-oil formulations acting as slow-release depots.

Cantrell, however, describes oil-in-water emulsions that probably act by direct immunostimulation; there is unlikely to be a depot effect from such formulations. In contrast to Cantrell, applicants' oil-in-water emulsion by definition must have "oil droplets substantially all of which are less than 1 micron in diameter" (claim 1). As shown in the accompanying Declaration and Figures 2a and 2b thereto, the Cantrell method produces oil droplets having a mean diameter of 22.4 microns, and thus is not "submicron" in nature. Figure 1 attached to the Declaration shows the striking difference in antibody titers when baboons were immunized with the HIV gp120 antigen and alum, or a Cantrell-type emulsion (supplied by the assignee of the Cantrell patent, Ribi ImmunoChem Research Inc.) compared with two of applicants' proprietary oil-in-water submicron emulsions, with one containing a muramyl peptide and the other lacking this component.

Thus, applicants' submicron formulations have unexpected and surprising properties when compared to the prior art. It is respectfully submitted that Claims 1-9, 29, and 36 are in condition for allowance.

Conclusion

If the Examiner believes that a telephone interview would expedite prosecution of this

application, she is invited to contact the undersigned at (510) 601-2708.

Respectfully submitted,

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